(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 October 2004 (21.10.2004)

PCT

(10) International Publication Number
WO 2004/090545 A3

(51) International Patent Classification[7]: G01N 33/574

(21) International Application Number:
PCT/EP2004/003877

(22) International Filing Date: 13 April 2004 (13.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/462,723 14 April 2003 (14.04.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
11 August 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS FOR TREATING PROLIFERATIVE DISEASES AND FOR MONITORING THE EFFECTIVENESS OF TREATMENT OF PROLIFERATIVE DISEASES

(57) Abstract: The present invention relates to phosphoproteins useful as biomarkers for identifying and treating patients suffering from diseases characterized by an aberrant MAP kinase signaling pathway, for example proliferative diseases like certain cancers, monitoring the efficacy of treatment of patients having the disease by administering Raf kinase inhibitors and diagnosing the disease in patients.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/003877

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TORRES KEILA ET AL: "Translation of taxol-induced Raf-1 kinase activation into stathmin phosphorylation and reorganization of the microtubule cytoskeleton" MOLECULAR BIOLOGY OF THE CELL, vol. 10, no. SUPPL., November 1999 (1999-11), page 264a, XP009038310 & 39TH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CELL BIOLOGY; WASHINGTON, D.C., USA; DECEMBER 11-15, 1999 ISSN: 1059-1524 the whole document	1-25

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 2004	20 06. 2005
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Thumb, W

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LOVRIC JOSIP ET AL: "Activated Raf induces the hyperphosphorylation of stathmin and the reorganization of the microtubule network" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 35, 28 August 1998 (1998-08-28), pages 22848-22855, XP002301398 ISSN: 0021-9258 the whole document	1-25
Y	MARKLUND ULRICA ET AL: "Multiple signal transduction pathways induce phosphorylation of serines 16, 25, and 38 of oncoprotein 18 in T lymphocytes" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 268, no. 34, 1993, pages 25671-25680, XP002301399 ISSN: 0021-9258 cited in the application abstract	1-25
Y	WO 02/24680 A (DEAN DAVID KENNETH ; SMITHKLINE BEECHAM PLC (GB); TAKLE ANDREW KENNETH) 28 March 2002 (2002-03-28) page 1 - page 2	1-25
Y	LAIRD A DOUGLAS ET AL: "Oncoprotein signalling and mitosis" CELLULAR SIGNALLING, vol. 9, no. 3-4, 1997, pages 249-255, XP002301400 ISSN: 0898-6568 page 252, column 2, paragraph 3 - page 253, column 1, paragraph 1 figure 1	1-25
A	WO 01/76570 A (TRANSMIT GMBH ; LUDWIG STEPHAN (DE); PLESCHKA STEPHAN (DE)) 18 October 2001 (2001-10-18) the whole document	1-25
A	DAVIES H ET AL: "MUTATIONS OF THE BRAF GENE IN HUMAN CANCER" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 417, no. 6892, 27 June 2002 (2002-06-27), pages 949-954, XP001188240 ISSN: 0028-0836 cited in the application the whole document	1-25

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/003877

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROBINSON M J ET AL: "Mitogen-activated protein kinase pathways" CURRENT OPINION IN CELL BIOLOGY, CURRENT SCIENCE, LONDON, GB, vol. 9, no. 2, 1997, pages 180-186, XP002238980 ISSN: 0955-0674 the whole document in particular Figure 1	1-25

INTERNATIONAL SEARCH REPORT

International application No.
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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-8 (partially)
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the biological mechanism underlying said method.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-25 (partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-25 (partially)

A method for monitoring a disease characterized by an aberrant MAP kinase signaling pathway, a method for treating said disease, a method for monitoring the progression of said disease and a method for monitoring the efficacy of treatment of said disease, said methods comprising detecting the level of phosphorylation of oncoprotein 18 (Op18).

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2. claims: 1-25 (partially)

A method for monitoring a disease characterized by an aberrant MAP kinase signaling pathway, a method for treating said disease, a method for monitoring the progression of said disease and a method for monitoring the efficacy of treatment of said disease, said methods comprising detecting the level of phosphorylation of oncoprotein EMS1.

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3. claims: 1-25 (partially)

A method for monitoring a disease characterized by an aberrant MAP kinase signaling pathway, a method for treating said disease, a method for monitoring the progression of said disease and a method for monitoring the efficacy of treatment of said disease, said methods comprising detecting the level of phosphorylation of Heat-shock 110kD protein.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/003877

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